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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,095	HONE, DAVID	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 3,4,15 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14,16-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-14 and 16-20, drawn to a DNA vaccine comprising at least one genetic sequence encoding a mutant ADP-ribosyltransferase toxin (mART); at least one genetic sequence encoding an antigen, and a method of vaccinating a patient comprising introducing into a patient at least one genetic sequence encoding a mutant ADP-ribosyltransferase toxin; and at least one genetic sequence encoding an antigen, classified in class 514, subclass 44.

II. Claim 15, drawn to a vaccine comprising at least one genetic sequence encoding a mutant ADP-ribosyltransferase toxin (mART); and an antigen, classified in class 424, subclass 184.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I, and II are patentably distinct inventions for the following reasons. In the instant case the different invention of group I is to a DNA vaccine comprising at least one genetic sequence encoding a mutant ADP-ribosyltransferase toxin; at least one genetic sequence encoding an antigen, and a method of vaccinating a patient comprising introducing into a patient at least one genetic sequence encoding a mutant ADP-ribosyltransferase toxin; and at least one genetic sequence encoding, while the invention of group II is to a vaccine comprising at least one genetic sequence encoding a mutant ADP-ribosyltransferase toxin; and an antigen. The invention

of group I comprises the administration of at least two different DNA sequences, mART and a sequence encoding an antigen, The invention of group II comprises the administration of at least one mART DNA sequence and a single antigen. The antigen of group II could be a protein, a lipid or a nucleic acid sequence. Thus, the invention of group II encompasses a much broader range of antigens than the invention of Group I, rendering the two inventions patentably distinct. Neither invention requires the other.

Furthermore, searching the inventions of groups I -II together would impose a serious search burden. In the instant case, the search of a DNA vaccine and a genetic sequence encoding an antigen, and a vaccine composition comprising a genetic sequence and an antigen are not coextensive. The vaccine composition of group I comprises searching a nucleic acid encoded antigen, while the vaccine composition of group II comprises searching a protein, lipid or nucleic acid. Proteins, even though coded by nucleic acids, are substantially different in structure and function from nucleic acids. Proteins and nucleic acids are made through substantially different processes and are made up of structurally different molecules. The literature for proteins is not co-extensive with the literature for nucleic acids. Finally, the inventions of groups I -II have a separate status in the art as shown by their different classifications. As such, it would be burdensome to search the inventions of groups I-II together.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, different classification, and different search requirements, restriction for examination purposes as indicated is proper.

This application contains claims directed to the following patentably distinct species of the claimed invention. The invention of groups I and II list the following patentably distinct species of a mutant ADP-ribosyltransferase toxin derived from:

a) cholera toxin

b) pertussis toxin

c) heat labile toxin of enterotoxigenic *E. coli*

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-20 are generic.

This application contains claims directed to the following patentably distinct species of the claimed invention. The invention of groups I and II list the following patentably distinct species of a ADP-ribosyltransferase toxin mutations:

a) R7K

b) R13H

c) E29H

d) H35R

e) L41F

f) F50S

g) S61K

h) S63K

i) S63Y

j) V53D

k) V97K

l) Y104K

m) P106S

n) H171Y

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-20 are generic.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Michael Whitham on October 15, 2004 a provisional election was made with traverse to prosecute the invention of group I, claims 1-14 and 16-20 and the species of mART derived from cholera toxin containing the L41F mutation. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3,4 and 15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicant should note that the claims have only been examined to the extent to which they read on the elected subject matter.

Election with Traverse

Applicant timely traversed the restriction (election) requirement in the telephone interview on October 15, 2004. Applicant has not provided any grounds for the traversal. This is not found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Acknowledgment is made of applicant's claim for priority to provisional Application No: 60/477, 460, filed on 02/14/03.

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include

the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. Applicant needs to update the dates of the provisional application. Specifically application 60/477, 460, must clearly state in the specification that it was filed on 02/14/03.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an

unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Specification

The specification is objected to because the attempt to incorporate subject matter into this application by reference to the "Appendix" is improper because a reference to an "Appendix" is not a proper citation of any type of reference, whether a patent, foreign patent publication or non-patent literature. Specifically, see the page 12, line 11 of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for a DNA vaccine comprising at least one genetic sequence encoding a mART derived from cholera toxin containing the L41F mutation, and at least one genetic sequence encoding an antigen; and a method of vaccinating a patient with the DNA vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to perform the invention commensurate in scope with these claims.

Claims 1-14 and 16-20 continue to read on any of the ADP-ribosyltransferase toxin mutations listed in claim 5. However, following Restriction/Election of species the claims have only been examined on a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation.

The claims read on a DNA vaccine comprising any and all variants, mutants and fragments of mART derived from cholera toxin, as long as the mART includes a L41F mutation. A vaccine is defined in the art as a composition capable of preventing or treating an infectious disease. The specification does not provide enablement for any and all variants, mutants or fragments of mART derived from cholera toxin. Zhang et al. teaches that cholera toxin (CT) consists of a heterohexameric AB_5 complex with an A1 subunit responsible for ADP-ribosylation {Zhang et al. (1995) J. Mol. Biol. 251:563-573, pg. 251, abstract}. The specification only describes single amino acid mutants of a CtxA1 (ART), consisting of 582 bp, derived from cholera toxin (pgs. 34 & 37). The specification does not indicate if the 582 bp sequence encodes a full length CtxA1 or a fragment thereof. Further, while the specification contemplates a mutant

cholera mART containing L41F, there are no working examples describing the making or use of a DNA vaccine comprising a genetic sequence of L41F mART.

The specification fails to disclose how to predict which single amino acid mutations of the A1 subunit of CT render it non-toxic yet immunogenic. No guidance is provided on how to select these single acid mutations without trial and error. Zhang et al. teaches the crystal structure of the A1 chain of the cholera toxin (CtxA1 or ART) (pg. 251, abstract). Zhang provides guidance that the residues implicated in catalyzing ADP-ribosylation line the left wall of a binding cleft from 65-77 (pg. 567, Figure 6). Neither the specification, nor the literature known in the art at the time of publication indicate that a genetic sequence encoding an L41F mART is predicted to be a useful adjuvant for DNA vaccines. Bagley et al. teaches that wildtype CT is extremely toxic to humans when administered orally {Bagley et al. (2003) Vaccine 21:3335-3341, pg. 336, col. 1, pgph 2}. Yamamoto et al. concurs stating that in the past CT was considered to be an unsuitable adjuvant for use in humans because it causes sever diarrhea {Yamamoto et al. (1999) J. Immunology 162:7015-7021}. Zhang teaches that the A1 subunit of CT is responsible for CT's catalytic activity and thus it's toxicity (pg. 567). The specification does not teach that a genetic sequence encoding L41F mART is non-toxic, is immunogenic or useful as an adjuvant for DNA vaccines.

The specification does not provide any working examples describing the making or administration of a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen. A vaccine is defined in the art as a composition used to prevent or treat an infectious disease. The specification does not disclose any working examples showing that a DNA vaccine comprising

any mART is capable of preventing or treating any disease. Several single amino acid mutations of the A1 subunit of CT are described in the art. Yamamoto et al. teaches two CT-A1 subunit mutant cDNAs with single amino acid mutations, S61F and E112K, that have lost their cytotoxic properties yet retain there usefulness as adjuvants {Yamamoto et al. (1997) J. Exp. Med. 185:1203-1210; Abstract}. Dolan et al. teaches a cDNA with a F54T mutation in A1 subunit of CT that causes a loss of function {Dolan et al. (2000) Biochemistry 39:8266-8275; Abstract}. However, these molecules have not been described as components of working vaccines. All of the working examples are to either the E29H or S63K mART cholera toxin mutant. The specification does not disclose that these two amino acids are located in an essential functional domain. Further, the location of L41F is not correlated with any essential functional domain or with any function associated with E29H or S63K. No examples are presented of DNA vaccines with multiple mARTs or multiple antigens.

The working examples describe two vectors that comprise a genetically encoded mART and an antigen: 1) pCtxA1-E29H (with the CMV promoter), which comprises genetic sequences of the E29H mART and the receptor binding domain of protective antigen of *Bacillus anthracis*; 2) pOGL1-A1-S63K (with the CMV promoter), which comprises genetic sequences of the S63K mART and gp120. The specification does not describe any assessment of the ability of the pCtxA1-E29H vector to protect against or treat an anthrax infection. Further, there are no working examples describing any immune response induced by vaccination with the pCtxA1-E29H vector. There is a single working example describing an increase in serum IgG in mice in response to treatment with the pOGL1-A1-S63K vector. However, there is no indication that the IgG increase, even if observed in a mammal susceptible to HIV, would provide protection

against an HIV infection. The specification does not disclose that either the pCtxA1-E29H vector or the pOGL1-A1-S63K vector can prevent or treat an infectious disease.

Emini et al teaches that even though a number of neutralizing antibodies to HIV have been identified this knowledge has not permitted the successful design of vaccine immunogens that can routinely elicit such antibody responses {Emini et al. (2004) Science 304:1913-1914; pg. 1914, col. 1, pgph1}. There are presently no effective HIV vaccines available due to the obstacles created by HIV's ability to evade the immune system due to in part to continuous mutations in its genome leading to high intra-individual and population based virus variability (Emini pg. 1913, col.2, pgph 1). The specification does not provide any evidence to suggest that the pOGL1-A1-S63K vector is able to prevent or treat HIV. Given the breadth of the claims, the lack of guidance in the specification on any DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen, the lack of working examples showing that a DNA vaccine comprising a genetic sequence encoding any mART and an antigen are capable of preventing or treating an infectious disease, and the art recognized difficulties in designing an HIV vaccine, the skilled practitioner would be unable to practice the invention as claimed without arduous and extensive experimentation.

The specification also does not provide an enabling disclosure for using any expression vector/promoter combination to express a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen *in vivo*. The claims read on any and all vectors, including plasmids, viral vectors, retroviral vectors, naked DNA and naked RNA. The claims also read on any and all

promoters, including SV40, CMV, or SV2. Verma et al. states that, the Achilles heel of gene therapy is gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, col. 3, pgph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems are entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trail and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Thus, given the lack of guidance in the specification on how to construct any vector with any promoter or promoters comprising a DNA vaccine comprising a genetic sequence encoding a mART derived from cholera toxin containing a L41F mutation and a genetic sequence encoding an antigen, a skilled artisan would be unable to practice the invention, except with a DNA plasmid containing the CMV promoter for *in vivo* transfection, without arduous and

extensive experimentation.

Claims 1-14 and 16-20 are free of the prior art of record because the art, while describing other mARTs does not describe L41F.

Please note that the closest prior art is exemplified by US Patent No: 60,019,982 (2000), hereafter referred to as Clements et al., by Yamamoto et al. {Yamamoto et al. (1997) J. Exp. Med. 185:1203-1210}, and by Dolan et al. {Dolan et al. (2000) Biochemistry 39: 8266-8275}. Clements et al. teaches a mutant form of heat labile enterotoxin produced by *E. coli* that has lost its toxicity yet retained it's immunogenicity and is useful as an adjuvant (col. 8, subsection 3). Clements et al. also teaches that heat treated CT protein loses it's toxicity yet remains a potent oral immunogen (col. 3). Yamamoto et al. teaches two CT-A subunit mutant cDNAs with single amino acid mutations, S61F and E112K, that have lost their cytotoxic properties yet retained their usefulness as adjuvants (Abstract). Dolan et al. teaches a cDNA with a F54T mutation in A1 subunit of CT that causes a loss of function (Abstract).

No Claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703)-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information

Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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